Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2012 January ; 15(1): 64–70. doi:10.1097/MCO.0b013e32834d1a08.

Arginases and Arginine Deficiency Syndromes

Sidney M. Morris Jr.

Department of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Abstract

Purpose of review—Many physiologic and pathophysiologic processes are modulated by arginine availability, which can be regulated by arginase. An understanding of the conditions that result in elevated arginase activity as well as the consequences of arginine deficiency is essential for design of effective nutritional support for disease. This review will emphasize recent findings regarding effects of plasma arginase and arginine deficiencies in disease.

Recent findings—Elevations in plasma arginase, derived primarily from hemolysis of red blood cells or liver damage, that are associated with arginine deficiency have been identified in an increasing number of diseases and conditions. Arginine insufficiency not only can activate a stress kinase pathway that impairs function of T lymphocytes but it also can inhibit the mitogen-activated protein kinase signaling pathway required for macrophage production of cytokines in response to bacterial endotoxin/lipopolysaccharide.

Summary—There are at least two broad categories of arginine deficiency syndromes, involving either T cell dysfunction or endothelial dysfunction, depending on the disease context in which arginine deficiency occurs. There is limited information regarding the safety and efficacy of supplementation with arginine or its precursor citrulline in ameliorating arginine deficiency in specific diseases, indicating the need for further studies.

Keywords

arginine; arginase; nitric oxide; endothelial dysfunction; T cell dysfunction

Introduction

The amino acid arginine is of particular interest because it plays a variety of roles in many different cell types. In addition to serving as substrate for protein synthesis, arginine is a precursor to nitric oxide (NO), polyamines, proline, glutamate, creatine, and agmatine[1]. Consequently, deficiencies of arginine have the potential to disrupt many cellular and organ functions.

In principle, there are three conditions that could result in arginine deficiency: dietary deficiency of arginine either by starvation or by ingesting a diet severely deficient in arginine (although the latter has not been found to result in arginine deficiency in healthy adults), increased catabolism of arginine, usually via arginase, and decreased rate of endogenous arginine synthesis. Conditions involving tissue or cellular arginine deficiency due to localized increases in arginase activity—particularly in macrophages in infection and inflammation—are numerous and thus beyond the scope of this review. Dietary arginine deficiency will not be discussed here, nor will deficiencies in arginine synthesis, aspects of

which were recently reviewed in this journal[2]. This review will emphasize arginine deficiencies associated with increased plasma arginase activity in humans.

Two arginase isozymes are expressed in humans and other mammals: arginase I, which is cytosolic and expressed at high levels in liver as a component of the urea cycle, and arginase II, which is mitochondrial and expressed in moderate levels in kidney[3]. Either or both isozymes can be expressed also in many other cell types and are inducible by a variety of stimuli, depending on cell type[4, 5]. Enzymatic properties of the isozymes are very similar, and both efficiently catalyze conversion of arginine to ornithine and urea.

Elevated plasma arginase and arginine deficiency

A low level of arginase is normally present in plasma of healthy individuals but can become elevated in certain conditions or diseases (Table 1). As plasma arginase activity is not routinely assayed by clinical chemistry laboratories, the full range of conditions in which it becomes elevated is not yet known. Plasma arginine concentrations were not measured for all conditions in which plasma arginase was increased (Table 1). Pathophysiologic consequences associated with arginine deficiency have not been demonstrated for all disorders in which elevated plasma arginase has been reported. Thus, for some disorders elevated plasma arginase levels may be more important as a marker of organ damage or disease than as a mechanistic component of a disease process. A possible case in point is liver resection, following which plasma arginase levels are moderately increased without an attendant reduction in plasma arginine[15]. Whether elevated plasma or tissue arginase activities play a role in arginine deficiency in other disorders remains to be determined. For example, plasma arginine levels in adolescents and adults with phenylketonuria are about 30% lower than in age-matched controls[21]. There are conflicting reports regarding plasma arginine levels in sepsis, but a recent meta-analysis concluded that plasma arginine concentrations are indeed reduced in sepsis in the absence of trauma or surgery[22]. The underlying basis and pathophysiologic consequences of the apparent deficiencies in these two examples as well as in other cases remain to be elucidated.

Clinicians and investigators should be aware of certain aspects of arginase biology that must be taken into consideration when measuring plasma arginine concentration. First, enzymatically active arginase I is present in red blood cells of humans (note that there is negligible arginase in rodent red blood cells), is released upon hemolysis, and remains active following release into the plasma. Although delayed or improper handling of blood samples from healthy individuals can result in artifactually low plasma arginine values[23], this is of particular concern for samples from patients with chronic hemolytic diseases or blood samples in which hemolysis may have occurred during collection or processing. Because extracellular levels of arginase gradually increase over time in stored human blood[24–26], this also may result in decreased values of plasma arginine in blood samples taken shortly after transfusion, depending on the volume of transfused blood and length of storage prior to transfusion. More importantly, the arginase, hemoglobin and other cellular components released in stored blood over time have the potential for detrimental effects in patients transfused with blood that has been stored for long periods[24, 26]. Second, the liver contains the largest amount of arginase I in the body. Thus, any disease or damage to the liver (including liver transplantation) that results in elevated plasma levels of transaminases or other liver enzymes also will result in elevated plasma levels of arginase I[15, 16, 27]. In summary, investigators must take particular care with collection and processing of blood samples but especially from patients with any condition associated with elevated plasma arginase (e.g., see Table 1). In order to minimize catabolism of arginine following collection, samples should be chilled and expeditiously processed to obtain plasma, which should be immediately frozen or deproteinized.

High levels of arginase are found in plasma of individuals with chronic hemolytic anemias, such as sickle cell disease[6, 28] and paroxysmal nocturnal hemoglobinuria[19]. Circulating levels of arginine are significantly reduced in sickle cell patients[6, 29, 30]. Although this is consistent with elevated plasma arginase activity in these individuals, the possibility that elevated expression of arginase in tissues of sickle cell patients also may play a role in arginine catabolism cannot be ruled out. Importantly, ratios between plasma concentrations of arginine and its metabolites have proven more useful as biomarkers in some disorders than have plasma concentrations of arginine alone. Low values of the ratio of plasma arginine/(plasma ornithine + citrulline), which has been termed the “global arginine bioavailability ratio” (GABR), represent an independent risk factor for morbidity and mortality in sickle cell patients[6, 31] and also are correlated with pulmonary hypertension in this patient population[6]. Low values of GABR also were associated with elevated plasma arginase activities in wild type and ApoE-deficient mice fed an atherogenic high cholesterol diet and also in ApoE-deficient mice fed a high fat diet[32]. Interestingly, these diets did not result in decreased plasma arginine level, indicating in this case that the GABR was a more sensitive indicator of dysregulated arginine metabolism than was plasma arginine concentration alone. Although plasma arginase was not measured, a recent clinical study found that reduced values of GABR were associated also with increased risk of cardiovascular disease in individuals without sickle cell disease[33]. These three examples indicate that the GABR ratio may be a useful biomarker in assessing risk of some types of cardiovascular disease. However, additional studies are clearly needed to evaluate the relative utility and significance of GABR values in different patient populations. This point is underscored by two studies. First, GABR values in asthma patients were greater than in healthy controls, despite greater plasma arginase levels in the asthma group[8]. Second, another group reported that GABR values were not altered in patients with severe sepsis, even though plasma arginine concentrations were significantly reduced[34]. Instead, the plasma arginine/dimethylarginine ratio was associated with severity of illness and clinical outcomes.

It is important to note that elevations in plasma arginase are not always associated with reductions in plasma arginine. Although an early study found elevated plasma arginase and decreased plasma arginine in asthma[7], a recent study of a much larger group of asthma patients found no decrease in plasma arginine or GABR despite increases in plasma arginase[8]. Differences in the patient populations may have contributed to the different results regarding plasma arginine. As another example, plasma arginine increased in cirrhotic patients with progressive renal dysfunction despite increases also in plasma arginase I protein[35]. The authors speculated that the increased plasma arginase was simply not sufficient to compensate for the increases in plasma arginine. As plasma arginase activity was not determined, it also is possible that the arginase I protein in plasma may not have been active.

Arginine deficiency and endothelial dysfunction

An increased incidence of pulmonary hypertension in sickle cell patients is associated with increasing severity of arginine deficiency—particularly as indicated by reduced GABR[6]—and this is likely to be true also for other chronic hemolytic anemias[36]. It is important to note that arginine deficiency in these diseases occurs in the context of chronically elevated cell-free hemoglobin, which is an effective scavenger of NO, as well as increased oxidative stress. Thus, the endothelial dysfunction and reduced NO bioavailability in sickle cell disease cannot be attributed solely to arginine deficiency.

Interestingly, malaria has similarities with sickle cell disease with regard to pathophysiology: increased hemolysis, reduced plasma arginine concentrations, increased

plasma arginase (but not as great as in sickle cell disease), and endothelial dysfunction[10–12]. Compared to healthy adults, the half-life of infused arginine is reduced in patients with malaria, consistent with increased catabolism, likely via arginase[37].

Arginine deficiency and immune cell dysfunction

Studies with cultured cells have demonstrated that arginine deficiency due to arginase can result in T cell dysfunction via reduced expression of the CD3zeta chain of the T cell receptor complex[38] and cell cycle arrest[39], suggesting that similar effects might be observed in patients with arginine deficiency. Patients with renal cell carcinoma had reduced plasma arginine and also had reduced levels of the CD3zeta chain of the T cell receptor complex[40]. In contrast, sickle cell patients with similar arginine deficiency did not exhibit similar T cell dysfunction[29]. These differences suggest that the context in which arginine deficiency occurs (e.g., presence or absence of hemolysis) is important in determining the pathophysiologic consequences of the deficiency.

T-cell dysfunction in chronic inflammatory disease and following physical injury (i.e., trauma or surgery) is associated with arginase activity in human granulocytes[41–44]. In fact, it has been proposed that arginine deficiency after physical injury is an important clinical syndrome[43].

Temporary suppression of the immune response during human pregnancy may represent a condition in which arginine deficiency secondary to elevated arginase activity is beneficial. Although arginine concentrations were not measured, arginase activity was elevated in neutrophils of pregnant women and in term placentas[17]. On the other hand, excessive increases in plasma or tissue arginase may contribute to development of preeclampsia[18]. Perhaps analogous to normal pregnancy, arginase-dependent depletion of arginine in cornea may be beneficial in minimizing rejection of corneal grafts[45].

Therapeutic application of arginase and arginine deficiency

There are conditions in which an arginine-deficient state may be desirable. For example, some tumor cells are auxotrophic for arginine and undergo cell cycle arrest and apoptosis in response to arginine deprivation. Thus, intravenous administration of pegylated derivatives of recombinant mammalian arginase or microbial arginine deiminase to create arginine deficiency is being explored as part of therapeutic strategies for some types of cancer (e.g., [46, 47].

Molecular basis for arginine deficiency syndromes

Endothelial dysfunction associated with arginine deficiency most likely reflects reduced availability of arginine as substrate for NO synthesis, although reduced expression of NO synthases also may occur in some cell types[48]. As noted above, the immune cell dysfunction associated with arginine deficiency involves cell cycle arrest and reduced expression of the zeta chain of the T cell receptor complex. Activation of the general control non-derepressible 2 (GCN2) kinase has recently been shown to underlie cell cycle arrest in T cells[39]. Indeed, several groups have demonstrated activation of the GCN2 kinase stress response pathway as a consequence of arginine deficiency in different cell types[39, 48, 49], indicating that this is an important NO-independent mechanism of response. Molecular and cellular responses to arginine deficiency are outlined in Figure 1. A major question arising from these studies is whether the threshold of reduced extracellular arginine concentration required to activate the GCN2 kinase pathway is the same for all cell types. Immune cell dysfunction resulting from arginine deficiency is not limited to T cells but also can involve macrophages. In addition to its effect on NO production, a recent study showed that arginine

insufficiency also impairs the mitogen-activated protein kinase signaling pathway required for macrophage production of cytokines in response to bacterial endotoxin/lipopolysaccharide[50].

Impact of arginine supplementation on arginine deficiency and associated symptoms of disease

If a specific disease condition is indeed due to arginine deficiency, it should be ameliorated or reversed by supplementation with arginine or its precursor citrulline. As a practical consideration, the efficacy of enteral arginine supplementation is limited by gastrointestinal discomfort following ingestion of large amounts of arginine and by the fact that a significant fraction of ingested arginine is catabolized by the small intestine before it is released into the portal blood. Citrulline has neither of these disadvantages, and recent studies have confirmed that supplementation with citrulline efficiently increases plasma arginine concentration in healthy adults without any reported side effects[51].

As discussed previously in this journal and elsewhere[52–55], the utility of arginine supplementation in patients remains highly controversial. This likely reflects heterogeneity of different patient populations studied, different formulations of supplements containing ingredients in addition to arginine, technical issues regarding accurate determination of plasma arginine concentrations, and gaps in basic knowledge regarding arginine metabolism in humans in health and disease.

Arginine supplementation has been used in only a limited number of human studies to test efficacy in overcoming arginine deficiency and associated symptoms in the diseases noted in this review. For example, arginine supplementation successfully increased plasma arginine levels in adult sickle cell patients, but it did not result in hematologic or physiologic improvement[56]. As indicated above, this likely reflects the importance of elevated cell-free hemoglobin and oxidative stress as contributing factors in endothelial dysfunction in this disease. More recently, supplementation with arginine and antioxidant vitamins reduced incidence of preeclampsia in women at high risk of this condition[57]; however, supplementation with arginine alone was not tested. Results of other studies suggest that evaluation of arginine supplementation in prevention or treatment of preeclampsia will not be straightforward [58, 59].

Arginase inhibitors represent a potential alternative for treatment of arginine deficiency. However, reversal or amelioration of a clinical condition by inhibition of arginase does not necessarily indicate that the condition is due to arginine deficiency because the condition instead could be the result of increased production of ornithine and its downstream metabolic products. To date, arginase inhibitors have not been evaluated in humans.

Conclusions

Arginine deficiency syndromes in humans fall into at least two broad categories, involving endothelial dysfunction or immune cell dysfunction. Although some clinical conditions may exhibit both types of arginine deficiency syndrome, most appear to primarily involve one or the other. In order to improve interpretation of clinical data, measurements of asymmetric dimethylarginine (ADMA) should be included more often in studies of arginine deficiency. The utility of arginine supplementation in treatment of arginine deficiency syndromes remains to be established.

Acknowledgments

This work was supported in part by National Institute of General Medical Sciences grant R01 GM57384.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Morris SM Jr. Arginine metabolism: boundaries of our knowledge. *J Nutr.* 2007; 137:1602S–1609S. [PubMed: 17513435]
2. Crenn P, Cynober L. Effect of intestinal resections on arginine metabolism: practical implications for nutrition support. *Curr Opin Clin Nutr Metab Care.* 2010; 13:65–9. [PubMed: 19915459]
3. Jenkinson CP, Grody WW, Cederbaum SD. Comparative properties of arginases. *Comp Biochem Physiol B Biochem Mol Biol.* 1996; 114:107–32. [PubMed: 8759304]
4. Mori M. Regulation of nitric oxide synthesis and apoptosis by arginase and arginine recycling. *J Nutr.* 2007; 137:1616S–1620S. [PubMed: 17513437]
5. Morris SM Jr. Recent advances in arginine metabolism: roles and regulation of the arginases. *Br J Pharmacol.* 2009; 157:922–30. [PubMed: 19508396]
6. Morris CR, Kato GJ, Poljakovic M, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. *JAMA.* 2005; 294:81–90. [PubMed: 15998894]
7. Morris CR, Poljakovic M, Lavrisha L, et al. Decreased arginine bioavailability and increased serum arginase activity in asthma. *Am J Respir Crit Care Med.* 2004; 170:148–53. [PubMed: 15070820]
8. Lara A, Khatri SB, Wang Z, et al. Alterations of the arginine metabolome in asthma. *Am J Respir Crit Care Med.* 2008; 178:673–81. [PubMed: 18635886]
9. Ogino K, Obase Y, Takahashi N, et al. High serum arginase I levels in asthma: its correlation with high-sensitivity C-reactive protein. *J Asthma.* 2011; 48:1–7. [PubMed: 21039185]
10. Yeo TW, Lampah DA, Gitawati R, et al. Impaired nitric oxide bioavailability and L-arginine reversible endothelial dysfunction in adults with falciparum malaria. *J Exp Med.* 2007; 204:2693–704. [PubMed: 17954570]
11. Weinberg JB, Lopansri BK, Mwaikambo E, Granger DL. Arginine, nitric oxide, carbon monoxide, and endothelial function in severe malaria. *Curr Opin Infect Dis.* 2008; 21:468–75. [PubMed: 18725795]
12. Janka JJ, Koita OA, Traore B, et al. Increased pulmonary pressures and myocardial wall stress in children with severe malaria. *J Infect Dis.* 2010; 202:791–800. [PubMed: 20662718]
13. Grasemann H, Schwiertz R, Grasemann C, et al. Decreased systemic bioavailability of L-arginine in patients with cystic fibrosis. *Respir Res.* 2006; 7:87. [PubMed: 16764721]
14. Bekpinar S, Gurdol F, Unlucerci Y, et al. Serum levels of arginase I are associated with left ventricular function after myocardial infarction. *Clin Biochem.* 2011 [Epub ahead of print].
15. van de Poll MC, Hanssen SJ, Berbee M, et al. Elevated plasma arginase-1 does not affect plasma arginine in patients undergoing liver resection. *Clin Sci (Lond).* 2008; 114:231–41. [PubMed: 17708746]
16. Ikemoto M, Tsunekawa S, Awane M, et al. A useful ELISA system for human liver-type arginase, and its utility in diagnosis of liver diseases. *Clin Biochem.* 2001; 34:455–61. [PubMed: 11676974]
17. Kropf P, Baud D, Marshall SE, et al. Arginase activity mediates reversible T cell hyporesponsiveness in human pregnancy. *Eur J Immunol.* 2007; 37:935–45. [PubMed: 17330821]
18. Bernardi F, Constantino L, Machado R, et al. Plasma nitric oxide, endothelin-1, arginase and superoxide dismutase in pre-eclamptic women. *J Obstet Gynaecol Res.* 2008; 34:957–63. [PubMed: 19012693]

19. Hill A, Rother RP, Wang X, et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2010; 149:414–25. [PubMed: 20230403]
20. Ogino K, Takahashi N, Takigawa T, et al. Association of serum arginase I with oxidative stress in a healthy population. *Free Radic Res*. 2011; 45:147–55. [PubMed: 20942574]
21. Sanayama Y, Nagasaka H, Takayanagi M, et al. Experimental evidence that phenylalanine is strongly associated to oxidative stress in adolescents and adults with phenylketonuria. *Mol Genet Metab*. 2011; 103:220–5. [PubMed: 21514861]
- **22. Davis JS, Anstey NM. Is plasma arginine concentration decreased in patients with sepsis? A systematic review and meta-analysis. *Crit Care Med*. 2011; 39:380–5. Using stringent criteria for inclusion in the meta-analysis, the authors conducted an extensive review of published studies and concluded that plasma arginine concentrations are significantly reduced in patients with sepsis in the absence of trauma or surgery. [PubMed: 21150584]
23. Davis JS, Darcy CJ, Piera K, et al. Ex-vivo changes in amino acid concentrations from blood stored at room temperature or on ice: implications for arginine and taurine measurements. *BMC Clin Pathol*. 2009; 9:10. [PubMed: 19941666]
24. Prins HA, Houdijk AP, Nijveldt RJ, et al. Arginase release from red blood cells: possible link in transfusion induced immune suppression? *Shock*. 2001; 16:113–5. [PubMed: 11508862]
25. Bernard A, Meier C, Lopez N, et al. Packed red blood cell-associated arginine depletion is mediated by arginase. *J Trauma*. 2007; 63:1108–12. [PubMed: 17993958]
26. Donadee C, Raat NJ, Kanas T, et al. Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. *Circulation*. 2011; 124:465–76. [PubMed: 21747051]
27. Ashamiss F, Wierzbicki Z, Chrzanowska A, et al. Clinical significance of arginase after liver transplantation. *Ann Transplant*. 2004; 9:58–60. [PubMed: 15759550]
28. Vilas-Boas W, Cerqueira BA, Zanette AM, et al. Arginase levels and their association with Th17-related cytokines, soluble adhesion molecules (sICAM-1 and sVCAM-1) and hemolysis markers among steady-state sickle cell anemia patients. *Ann Hematol*. 2010; 89:877–82. [PubMed: 20405289]
- *29. Scavella A, Leiva L, Monjure H, et al. Effect of L-arginine supplementation on immune responsiveness in patients with sickle cell disease. *Pediatr Blood Cancer*. 2010; 55:318–23. This study was the first to investigate whether arginine deficiency in sickle cell disease was associated with T cell dysfunction. Although there were differences in lymphocyte responses to mitogenic and antigenic stimuli, the authors found no differences in CD3zeta chain expression in sickle cell patients and controls. [PubMed: 20582959]
30. Sullivan KJ, Kissoon N, Sandler E, et al. Effect of oral arginine supplementation on exhaled nitric oxide concentration in sickle cell anemia and acute chest syndrome. *J Pediatr Hematol Oncol*. 2010; 32:e249–58. [PubMed: 20724949]
31. Cox SE, Makani J, Komba AN, et al. Global arginine bioavailability in Tanzanian sickle cell anaemia patients at steady-state: a nested case control study of deaths versus survivors. *Br J Haematol*. 2011 [Epub ahead of print].
- *32. Erdely A, Kepka-Lenhart D, Salmen-Muniz R, et al. Arginase activities and global arginine bioavailability in wild-type and ApoE-deficient mice: responses to high fat and high cholesterol diets. *PLoS One*. 2010; 5:e15253. This is the first demonstration in an animal model that reductions in GABR but not in plasma arginine are associated with increases in plasma arginase in response to diets that increase risk of atherosclerosis. [PubMed: 21151916]
33. Tang WH, Wang Z, Cho L, et al. Diminished global arginine bioavailability and increased arginine catabolism as metabolic profile of increased cardiovascular risk. *J Am Coll Cardiol*. 2009; 53:2061–7. [PubMed: 19477356]
- **34. Gough MS, Morgan MA, Mack CM, et al. The ratio of arginine to dimethylarginines is reduced and predicts outcomes in patients with severe sepsis. *Crit Care Med*. 2011; 39:1351–8. This careful study provides evidence that the ratio of arginine to dimethylarginines in plasma--but not plasma arginine or GABR values--is an independent predictor of hospital mortality and six-month survival of septic patients. [PubMed: 21378552]

35. Kayali Z, Herring J, Baron P, et al. Increased plasma nitric oxide, L-arginine, and arginase-1 in cirrhotic patients with progressive renal dysfunction. *J Gastroenterol Hepatol.* 2009; 24:1030–7. [PubMed: 19226382]
36. Morris CR, Vichinsky EP. Pulmonary hypertension in thalassemia. *Ann N Y Acad Sci.* 2010; 1202:205–13. [PubMed: 20712794]
37. Yeo TW, Rooslamati I, Gitawati R, et al. Pharmacokinetics of L-arginine in adults with moderately severe malaria. *Antimicrob Agents Chemother.* 2008; 52:4381–7. [PubMed: 18838585]
38. Zea AH, Rodriguez PC, Culotta KS, et al. L-Arginine modulates CD3zeta expression and T cell function in activated human T lymphocytes. *Cell Immunol.* 2004; 232:21–31. [PubMed: 15922712]
- *39. Rodriguez PC, Hernandez CP, Morrow K, et al. L-arginine deprivation regulates cyclin D3 mRNA stability in human T cells by controlling HuR expression. *J Immunol.* 2010; 185:5198–204. Activation of the GCN2 stress kinase response pathway was shown to be the mechanism that triggered cell cycle arrest in human T cells following arginine deprivation. [PubMed: 20889542]
40. Ochoa AC, Zea AH, Hernandez C, Rodriguez PC. Arginase, prostaglandins, and myeloid- derived suppressor cells in renal cell carcinoma. *Clin Cancer Res.* 2007; 13:721s–726s. [PubMed: 17255300]
41. Munder M, Schneider H, Luckner C, et al. Suppression of T-cell functions by human granulocyte arginase. *Blood.* 2006; 108:1627–34. [PubMed: 16709924]
42. Bryk JA, Popovic PJ, Zenati MS, et al. Nature of myeloid cells expressing arginase 1 in peripheral blood after trauma. *J Trauma.* 2010; 68:843–52. [PubMed: 19996805]
- **43. Zhu X, Herrera G, Ochoa JB. Immunosuppression and infection after major surgery: a nutritional deficiency. *Crit Care Clin.* 2010; 26:491–500. This review proposes that arginine deficiency following physical injury should be viewed as an important clinical syndrome that affects T cell function and NO production and that immune-enhancing diets containing arginine and also omega-3 fatty acids benefit physical injury patients by overcoming the arginine deficiency. [PubMed: 20643302]
44. Munder M. Arginase: an emerging key player in the mammalian immune system. *Br J Pharmacol.* 2009; 158:638–51. [PubMed: 19764983]
45. Fu H, Khan A, Coe D, et al. Arginine depletion as a mechanism for the immune privilege of corneal allografts. *Eur J Immunol.* 2011 [Epub ahead of print].
46. Glazer ES, Piccirillo M, Albino V, et al. Phase II study of pegylated arginine deiminase for nonresectable and metastatic hepatocellular carcinoma. *J Clin Oncol.* 2010; 28:2220–6. [PubMed: 20351325]
47. Hernandez CP, Morrow K, Lopez-Barcons LA, et al. Pegylated arginase I: a potential therapeutic approach in T-ALL. *Blood.* 2010; 115:5214–21. [PubMed: 20407034]
48. Lee J, Ryu H, Ferrante RJ, et al. Translational control of inducible nitric oxide synthase expression by arginine can explain the arginine paradox. *Proc Natl Acad Sci U S A.* 2003; 100:4843–8. [PubMed: 12655043]
- **49. Marion V, Sankaranarayanan S, de Theije C, et al. Arginine deficiency causes runting in the suckling period by selectively activating the stress kinase GCN2. *J Biol Chem.* 2011; 286:8866–74. Using a mouse model in which severe arginine deficiency is produced by expression of an arginase transgene in enterocytes, this study is the first to demonstrate that arginine deficiency can activate the GCN2 stress kinase pathway in vivo. [PubMed: 21239484]
- **50. Mieulet V, Yan L, Choisy C, et al. TPL-2-mediated activation of MAPK downstream of TLR4 signaling is coupled to arginine availability. *Sci Signal.* 2010; 3:ra61. This study is the first to demonstrate that arginine insufficiency impairs the macrophage response to bacterial endotoxin not only by reducing substrate for NO production but also by impairing activation of the mitogen-activated protein kinase pathway required for cytokine production. [PubMed: 20716763]
51. Moinard C, Nicolis I, Neveux N, et al. Dose-ranging effects of citrulline administration on plasma amino acids and hormonal patterns in healthy subjects: the Citrudose pharmacokinetic study. *Br J Nutr.* 2008; 99:855–62. [PubMed: 17953788]

52. Boger RH. L-Arginine therapy in cardiovascular pathologies: beneficial or dangerous? *Curr Opin Clin Nutr Metab Care*. 2008; 11:55–61. [PubMed: 18090660]
53. Coeffier M, Dechelotte P. Combined infusion of glutamine and arginine: does it make sense? *Curr Opin Clin Nutr Metab Care*. 2010; 13:70–4. [PubMed: 19904200]
- *54. Loehe F, Bruns CJ, Nitsch SM, Angele MK. The role of L-arginine following trauma and blood loss. *Curr Opin Clin Nutr Metab Care*. 2007; 10:80–7. This review of 35 published randomized clinical trials provides evidence that perioperative use of dietary supplements containing arginine and also omega-3 fatty acids for elective surgery reduced post-operative rates of infection and length of hospital stay. Although data on plasma arginase or arginine levels were not provided for the clinical trials, the authors speculated that the supplements had beneficial effects by overcoming arginine deficiency that likely occurred following surgery. [PubMed: 17143060]
55. Drover JW, Dhaliwal R, Weitzel L, et al. Perioperative use of arginine-supplemented diets: a systematic review of the evidence. *J Am Coll Surg*. 2011; 212:385–99. 399, e1. [PubMed: 21247782]
56. Little JA, Hauser KP, Martyr SE, et al. Hematologic, biochemical, and cardiopulmonary effects of L-arginine supplementation or phosphodiesterase 5 inhibition in patients with sickle cell disease who are on hydroxyurea therapy. *Eur J Haematol*. 2009; 82:315–21. [PubMed: 19215288]
57. Vadillo-Ortega F, Perichart-Perera O, Espino S, et al. Effect of supplementation during pregnancy with L-arginine and antioxidant vitamins in medical food on pre-eclampsia in high risk population: randomised controlled trial. *BMJ*. 2011; 342:d2901. [PubMed: 21596735]
58. Rytlewski K, Olszanecki R, Korbut R, Zdebski Z. Effects of prolonged oral supplementation with l-arginine on blood pressure and nitric oxide synthesis in preeclampsia. *Eur J Clin Invest*. 2005; 35:32–7. [PubMed: 15638817]
59. Neri I, Monari F, Sgarbi L, et al. L-arginine supplementation in women with chronic hypertension: impact on blood pressure and maternal and neonatal complications. *J Matern Fetal Neonatal Med*. 2010; 23:1456–60. [PubMed: 20958228]

Key points

Elevated levels of enzymatically active arginase in plasma occur in a wide range of disorders and may contribute to systemic arginine deficiency and associated pathophysiology.

Depending on severity, arginine deficiencies contribute to endothelial or T cell dysfunction.

Specific clinical consequences of arginine deficiency are highly dependent on the pathophysiologic context in which the deficiency occurs.

The global arginine bioavailability ratio (plasma arginine/ornithine + citrulline) is a biomarker of dysregulated arginine metabolism and also a risk factor for morbidity and mortality in some diseases.

Efficacy and safety of dietary supplements for treatment of arginine deficiencies in disease have not been rigorously studied and thus require further investigation.

Figure 1.

Examples of the cellular and molecular consequences of arginine deficiency. These examples are taken from the descriptions in the text and are not intended to be exhaustive. Increased superoxide synthesis by NOS isozymes is due to uncoupling of electron transfer when arginine is deficient. GCN2, general control non-derepressible 2; NOS, nitric oxide synthase.

Table 1

Examples of conditions in which plasma arginase is elevated in humans. n.d. = not determined.

Condition	Reduced plasma arginine	Reference
Sickle cell disease	√	[6]
Asthma	Mixed results	[7–9]
Malaria	√	[10–12]
Cystic fibrosis	√	[13]
Myocardial infarction	√	[14]
Liver transplant	√	[15]
Liver disease	n.d.	[16]
Normal pregnancy	n.d.	[17]
Preeclampsia	n.d.	[18]
Paroxysmal nocturnal hemoglobinuria	n.d.	[19]
Oxidative stress	n.d.	[20]